

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

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Nirmatrelvir is an orally bioavailable protease inhibitor that is active against M^{PRO}, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins.¹ It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.² Nirmatrelvir is packaged with ritonavir (as Paxlovid), a strong cytochrome P450 (CYP) 3A4 inhibitor and pharmacokinetic boosting agent that has been used to boost HIV protease inhibitors. Coadministration of ritonavir is required to increase nirmatrelvir concentrations to the target therapeutic range.

On December 22, 2021, the Food and Drug Administration issued an Emergency Use Authorization (EUA) for ritonavir-boosted nirmatrelvir for the treatment of patients with mild to moderate COVID-19 aged ≥ 12 years and weighing ≥ 40 kg who are within 5 days of symptom onset and at high risk of progressing to severe disease.^{3,4}

Recommendations

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends using **nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid)** orally twice daily for 5 days in nonhospitalized patients with mild to moderate COVID-19 aged ≥ 12 years and weighing ≥ 40 kg who are at high risk of disease progression;³ treatment should be initiated as soon as possible and within 5 days of symptom onset (**AIIa**).
- Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination.
- Before prescribing ritonavir-boosted nirmatrelvir, clinicians **should carefully review the patient's concomitant medications**, including over-the-counter medications, herbal supplements, and recreational drugs, to evaluate potential drug-drug interactions.
- The [Liverpool COVID-19 Drug Interactions website](#), Table A below, and the [EUA fact sheet for ritonavir-boosted nirmatrelvir](#) can be used to identify and manage drug-drug interactions.

For the Panel's recommendations on the order of preference for outpatient antiviral therapies and the prioritization of outpatient therapies when there are logistical or supply constraints, see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#).

Rationale

The EPIC-HR trial demonstrated that starting ritonavir-boosted nirmatrelvir treatment in nonhospitalized adults with mild to moderate COVID-19 within 5 days of symptom onset reduced the risk of hospitalization or death through Day 28 by 89% compared to placebo.⁴ This efficacy is comparable to the efficacies reported for sotrovimab (i.e., 85% relative reduction)⁵ and remdesivir (i.e., 87% relative reduction)⁶ and greater than the efficacy reported for molnupiravir (i.e., 30% relative reduction).⁷

Ritonavir-boosted nirmatrelvir is expected to be active against the B.1.1.529 (Omicron) variant of concern (VOC), although there is currently a lack of data on the clinical efficacy of ritonavir-boosted nirmatrelvir against this VOC.⁸⁻¹⁰ Because of the potential for significant drug-drug interactions with concomitant medications, this regimen may not be a safe choice for all patients (see below for more information).

Clinical Trial Data

The EPIC-HR study was a multinational randomized trial that compared the use of ritonavir-boosted nirmatrelvir given orally twice daily for 5 days to placebo in nonhospitalized patients aged ≥ 18 years

with mild to moderate COVID-19 who were at high risk of clinical progression. Eligible participants were randomized within 5 days of symptom onset, were unvaccinated against COVID-19, and had at least 1 risk factor for progression to severe disease.¹¹ Patients were excluded if they used medications that were either highly dependent upon CYP3A4 for clearance or strong inducers of CYP3A4.

A total of 2,246 participants enrolled in the trial. The mean age was 46 years, 51% of the participants were men, and 72% were White. Forty-seven percent of the participants tested negative for SARS-CoV-2 antibodies, and 66% started study treatment within 3 days of symptom onset.

Participants who were randomized within 3 days of symptom onset ($n = 1,379$) were included in the modified intention-to-treat (mITT) analysis. COVID-19-related hospitalizations and all-cause deaths occurred by Day 28 in 5 of 697 participants (0.72%) in the ritonavir-boosted nirmatrelvir arm and in 44 of 682 participants (6.5%) in the placebo arm. Among the 2,085 participants who were randomized within 5 days of symptom onset (mITT1 analysis), COVID-19-related hospitalizations and all-cause deaths occurred in 8 of 1,039 participants (0.77%) in the ritonavir-boosted nirmatrelvir arm and in 66 of 1,046 participants (6.3%) in the placebo arm (89% relative risk reduction; -5.6% estimated absolute reduction; 95% CI, -7.2% to -4.0%; $P < 0.001$). There were no deaths in the ritonavir-boosted nirmatrelvir arm and 13 deaths in the placebo arm.

Among the 2,224 participants who were included in the EPIC-HR safety analysis set (i.e., those who received at least 1 dose of either ritonavir-boosted nirmatrelvir or placebo), the adverse events that occurred more frequently in ritonavir-boosted nirmatrelvir recipients than in placebo recipients were dysgeusia (6% vs. 0.3%) and diarrhea (3% vs. 2%). Fewer ritonavir-boosted nirmatrelvir recipients discontinued the study drug due to an adverse event than placebo recipients (2% vs. 4%).

Additional Considerations

- Nirmatrelvir must be administered with ritonavir to achieve sufficient therapeutic plasma concentrations.
- Patients should complete the 5-day treatment course of ritonavir-boosted nirmatrelvir. It is unknown whether a shorter course is less effective or associated with the emergence of nirmatrelvir-resistant mutations.
- If a patient requires hospitalization after starting treatment, the full treatment course of ritonavir-boosted nirmatrelvir can be completed at the clinician's discretion.
- Ritonavir-boosted nirmatrelvir may be used in patients who are hospitalized for a diagnosis other than COVID-19, provided they have mild to moderate COVID-19, are at high risk of progressing to severe disease, and are within 5 days of symptom onset.
- There are no data on using combination antiviral therapies or combinations of antiviral agents and anti-SARS-CoV-2 monoclonal antibodies for the treatment of nonhospitalized patients with COVID-19. Clinical trials are needed to determine whether combination therapy has a role in the treatment of COVID-19.
- Severely immunocompromised patients can experience prolonged periods of SARS-CoV-2 replication, which may lead to rapid viral evolution. There are theoretical concerns that using a single antiviral agent in these patients may produce antiviral-resistant viruses. Additional studies are needed to assess this risk. The role of combination antiviral therapy in treating severely immunocompromised patients is not yet known.

Monitoring and Adverse Effects

The most common adverse effects of ritonavir-boosted nirmatrelvir are dysgeusia, diarrhea, hypertension, and myalgia.

The dose should be reduced to nirmatrelvir 150 mg with ritonavir 100 mg twice daily in patients with moderate renal impairment (i.e., those with an estimated glomerular filtration rate [eGFR] of ≥ 30 to < 60 mL/min). Ritonavir-boosted nirmatrelvir **is not recommended** in patients with an eGFR of < 30 mL/min until more data are available. The appropriate dose for patients with severe renal impairment has not been determined.

Ritonavir-boosted nirmatrelvir **is not recommended** for patients with severe hepatic impairment (i.e., Child-Pugh Class C), and it should be used with caution in patients with pre-existing liver diseases, liver enzyme abnormalities, or hepatitis. No pharmacokinetic or safety data are available for this patient population.

Considerations in Pregnancy

The EPIC-HR trial excluded pregnant and lactating individuals. Ritonavir has been used extensively during pregnancy in people with HIV, which suggests that it has an acceptable safety profile during pregnancy. Based on the mechanisms of action for both nirmatrelvir and ritonavir and the available animal data, the Panel would not withhold ritonavir-boosted nirmatrelvir from a pregnant patient if the potential benefits outweighed the potential risks.

Considerations in Children

Ritonavir-boosted nirmatrelvir is authorized for use in pediatric patients aged ≥ 12 years and weighing ≥ 40 kg. The EPIC-HR trial excluded persons aged < 18 years. The safety and efficacy of using ritonavir-boosted nirmatrelvir in pediatric patients has not been established in clinical trials.

Drug-Drug Interactions

Ritonavir-boosted nirmatrelvir has significant and complex drug-drug interactions, primarily due to the ritonavir component of the combination. Boosting with ritonavir, a strong CYP3A inhibitor, is required to increase the exposure of nirmatrelvir to a concentration that is effective against SARS-CoV-2. However, it may also increase concentrations of certain concomitant medications, thereby increasing the potential for serious and sometimes life-threatening drug toxicities. Additionally, ritonavir is an inhibitor, inducer, and substrate of various other drug-metabolizing enzymes and/or drug transporters.

Because ritonavir-boosted nirmatrelvir is the only highly effective oral antiviral for the treatment of COVID-19, drug interactions that can be safely managed **should not preclude** the use of this medication.

The treatment course of ritonavir-boosted nirmatrelvir for COVID-19 is 5 days. CYP3A4 inhibition occurs rapidly after initiating ritonavir, with maximum inhibition occurring within 48 hours.¹² After ritonavir is discontinued, 80% to 90% of CYP3A4 inhibition resolves within 3 days.¹³ The time to resolution of inhibition varies based on factors such as the patient's age; therefore, resolution may take longer in some individuals, such as in the elderly. When ritonavir is used for 5 days, its induction properties are less likely to be clinically relevant than when the drug is used chronically (e.g., in people who take HIV protease inhibitors). Both nirmatrelvir and ritonavir are substrates of CYP3A; thus, administering this treatment with or immediately after discontinuing medications that are strong inducers of CYP3A4 (e.g., rifampin) can lead to significant reductions in nirmatrelvir and ritonavir concentrations, which may decrease nirmatrelvir's effectiveness against SARS-CoV-2.

Guidance for Prescribers and Pharmacists

Identify Drug-Drug Interactions

- Before prescribing ritonavir-boosted nirmatrelvir, clinicians should carefully review the patient's concomitant medications, including over-the-counter medicines, herbal supplements, and

recreational drugs.

- Clinicians should refer to resources such as the [Liverpool COVID-19 Drug Interactions website](#), Table A below, and the [EUA fact sheet for ritonavir-boosted nirmatrelvir](#) for guidance regarding potential drug-drug interactions.
- Clinicians should consider consulting an expert (e.g., a pharmacist, HIV specialist, and/or the patient's specialist provider[s], if applicable), especially for patients who are receiving highly specialized therapies, such as antineoplastics, neuropsychiatric drugs, and certain immunosuppressants.
- Drug classes of particular concern are those that include drugs that are prone to concentration-dependent toxicities, including certain antiarrhythmics, oral anticoagulants, immunosuppressants, anticonvulsants, antineoplastics, and neuropsychiatric drugs.

Management Strategies for Drug-Drug Interactions

- Before administering ritonavir-boosted nirmatrelvir to a patient, clinicians should assess the potential risks and benefits of using this combination in that patient. In particular, clinicians should assess the availability of other equally effective COVID-19 treatment options that have lower risks of drug interactions.
- Clinicians should consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are receiving ritonavir-boosted nirmatrelvir. Potential strategies include:
 - Adjusting the dose of the concomitant medication,
 - Using an alternative to the concomitant medication,
 - Increasing monitoring for potential adverse reactions to the concomitant medication, *or*
 - Temporarily withholding the concomitant medication.
- Clinicians should use the chosen strategies for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 3 days after treatment completion. These strategies may need to be continued for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting concomitant medication has a long half-life or narrow therapeutic index.
- In settings where using these management strategies is not feasible or where the effectiveness of ritonavir-boosted nirmatrelvir may be compromised, consider using alternative COVID-19 therapies (see [Therapeutic Management of Nonhospitalized Adults With COVID-19](#)).
- The dose of ritonavir-boosted nirmatrelvir should not be adjusted to avoid or mitigate a drug-drug interaction with a concomitant medication.
- Patients on ritonavir- or cobicistat-boosted regimens that are used to treat HIV or hepatitis C virus should continue their treatment as indicated while receiving ritonavir-boosted nirmatrelvir. No dose adjustments are required.
- People who take certain recreational drugs, such as recreational fentanyl, will require careful monitoring for adverse effects if they are prescribed ritonavir-boosted nirmatrelvir.
- The EUA for ritonavir-boosted nirmatrelvir suggests that individuals who use products containing ethinyl estradiol for contraception should use a backup, nonhormonal contraceptive method because ritonavir-boosted nirmatrelvir has the potential to decrease ethinyl estradiol levels. However, the enzyme-inducing effects of ritonavir-boosted nirmatrelvir that would lead to lower hormone exposure are not expected to be clinically significant during 5 days of therapy and, therefore, would not be expected to decrease contraceptive effectiveness. In addition, ethinyl

estradiol is always combined with a progestin for contraception. Progestin concentrations are expected to remain similar or increase when ritonavir-boosted nirmatrelvir is used concomitantly with combined hormonal contraception, which maintains the effectiveness of the oral contraceptive.

Patient Counseling on Drug-Drug Interactions

- Patients should be informed of ritonavir-boosted nirmatrelvir's drug-drug interaction potential with concomitant medications, including over-the-counter medicines, herbal supplements, and recreational drugs.
- If a potential drug-drug interaction is identified, the patient should be informed about the interaction and alerted to the signs and symptoms of potential adverse effects.

Table A. Drug-Drug Interactions Between Ritonavir-Boosted Nirmatrelvir (Paxlovid) and Concomitant Outpatient Medications

This table is not a comprehensive list of all the drugs that may interact with ritonavir-boosted nirmatrelvir. This table focuses on concomitant medications that may be prescribed in the outpatient setting. Pharmacists or providers who have experience with prescribing ritonavir-boosted drugs (e.g., HIV specialists) should be consulted when monitoring and managing drug-drug interactions in patients with mild to moderate COVID-19 who are receiving ritonavir-boosted nirmatrelvir and who may be hospitalized for reasons that are not related to COVID-19.

Deviation from these recommendations may be appropriate in certain clinical scenarios. When significant drug-drug interactions are present, providers should exercise clinical judgment when assessing the risks and benefits of using ritonavir-boosted nirmatrelvir and determining the appropriate management strategies for these interactions.

The table below divides medications into 3 categories:

- Concomitant medications that require patients to receive an alternative COVID-19 therapy. For these drugs, drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits. This category includes:
 - Drugs that may cause significant toxicities due to CYP3A4 inhibition and that cannot be stopped or have their doses adjusted; *or*
 - Drugs that are strong CYP3A inducers and may significantly reduce the concentration of ritonavir and nirmatrelvir, potentially leading to a loss of virologic response. Ritonavir-boosted nirmatrelvir cannot be initiated immediately after discontinuing CYP3A inducers due to the delayed offset of induction.
- Concomitant medications that should be temporarily withheld, if clinically appropriate. If withholding is not clinically appropriate, temporarily switching to an alternative concomitant medication or using an alternative COVID-19 therapy should be considered.
- Concomitant medications that should receive dose adjustments. Patients should be monitored closely for adverse effects. If the dose of the concomitant medication cannot be adjusted, consider withholding the medication (if clinically appropriate) or using an alternative concomitant medication or an alternative COVID-19 therapy.

Prescribe an Alternative COVID-19 Therapy

For cases where drug-drug interaction management strategies are not possible or feasible, or the potential risks of such strategies outweigh the potential benefits.

Amiodarone	Flecainide	Propafenone
Apalutamide	Glecaprevir/pibrentasvir	Quinidine
Bosentan	Ivabradine	Rifampin
Carbamazepine	Lumacaftor/ivacaftor	Rifapentine
Clopidogrel ^a	Lumateperone	Sildenafil for PH
Clozapine	Lurasidone	St. John's wort
Disopyramide	Meperidine (pethidine)	Tadalafil for PH
Dofetilide	Midazolam (oral)	Tolvaptan
Dronedarone	Phenobarbital	Vardenafil for PH
Enzalutamide	Phenytoin	Voclosporin
Eplerenone	Pimozide	
Ergot derivatives	Primidone	

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

For guidance on restarting the concomitant medication, consult the [Liverpool COVID-19 Drug Interactions website](#).^b If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Alfuzosin	Estazolam ^d	Rosuvastatin
Aliskiren	Everolimus ^f	Salmeterol
Atorvastatin	Finerenone	Sildenafil
Avanafil	Flibanserin	Simvastatin
Chemotherapy ^c	Flurazepam ^d	Sirolimus ^f
Clonazepam ^d	Lomitapide	Suvorexant
Clorazepate ^d	Lovastatin	Tacrolimus ^f
Colchicine ^e	Naloxegol	Ticagrelor
Diazepam ^d	Ranolazine	Triazolam ^d
Eletriptan	Rimegepant	Ubrogepant
Erythromycin	Rivaroxaban ^g	Vorapaxar

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the [Liverpool COVID-19 Drug Interactions website](#)^b for guidance. If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Alprazolam ^d	Darifenacin	Pimavanserin
Amlodipine	Digoxin	Quetiapine
Apixaban	Elexacaftor/tezacaftor/ivacaftor	Rifabutin
Aripiprazole	Eluxadoline	Riociguat
Brexiprazole	Fentanyl	Saxagliptin
Buspirone	Iloperidone	Sildenafil for ED
Cariprazine	Itraconazole	Ruxolitinib
Chlordiazepoxide ^d	Ivacaftor	Tadalafil for ED
Cilostazol	Ketoconazole	Tamsulosin
Clarithromycin	Maraviroc	Tezacaftor/ivacaftor
Clobazam ^d	Mexiletine	Trazodone
Cyclosporine ^f	Oxycodone	Vardenafil for ED

^a Reduced effectiveness of clopidogrel is likely. Do not coadminister clopidogrel in patients who are at a very high risk of thrombosis (e.g., those who are within 6 weeks of coronary stenting); consider prescribing an alternative antiplatelet (i.e., prasugrel) or an alternative COVID-19 therapy. For other indications, it may be acceptable to continue clopidogrel if the benefit of ritonavir-boosted nirmatrelvir treatment outweighs the risk of reduced clopidogrel effectiveness.

^b Additional resources include the [EUA fact sheet for ritonavir-boosted nirmatrelvir](#) and the FDA prescribing information for the concomitant medication. These may be consulted for medications that are not found on the Liverpool COVID-19 Drug Interactions website.

- ^c Ritonavir-boosted nirmatrelvir may increase concentrations of certain anticancer agents, leading to an increased potential for drug toxicities. These anticancer agents include kinase inhibitors (e.g., abemaciclib, ceritinib, dasatinib, ibrutinib, neratinib, nilotinib), the IDH1 inhibitor ivosidenib, the BCL-2 inhibitor venetoclax, and vinca alkaloids (e.g., vinblastine, vincristine). Please refer to the prescribing information for the anticancer agent and consult the patient's specialist provider. Avoid concomitant administration of ritonavir-boosted nirmatrelvir with ibrutinib, neratinib, ivosidenib, or venetoclax.
- ^d Abrupt discontinuation or rapid dose reduction of benzodiazepines may precipitate acute withdrawal reactions.¹⁴ The risk is greatest for patients who have been using higher doses of benzodiazepines over an extended period of time.
- ^e Colchicine is contraindicated in patients with severe hepatic or renal impairment due to the potential for serious or life-threatening reactions.
- ^f Before prescribing ritonavir-boosted nirmatrelvir to a patient who is receiving this immunosuppressant, consult the patient's specialist provider(s). This immunosuppressant has significant drug-drug interaction potential with ritonavir, and close monitoring may not be feasible. See [this statement from the American Society of Transplantation](#) for more information.
- ^g If the patient has a high risk of arterial or venous thrombosis (e.g., those who are within 3 months of a stroke, those with a CHA2DS2-VASc score of 7–9, those who are within 1 month of a pulmonary embolism), the patient's primary or specialty provider should be consulted; consider using an alternative anticoagulant or COVID-19 therapy.

Key: BCL-2 = B cell lymphoma 2; CYP = cytochrome P450; ED = erectile dysfunction; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IDH1 = isocitrate dehydrogenase-1; PH = pulmonary hypertension

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